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Gymnema sylvestre for Diabetes Mellitus: A Systematic Review

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ABSTRACT

Across the globe, there are an estimated 150 million people suffering from diabetes mellitus. Each of these people is at increased risk of developing a number of complications, each of which are associated with a reduction in quality of life and an increase in individual morbidity and mortality. However, despite these psychosocial implications, as well as the financial burden associated with the management of the disease, existing treatment options are costly, and have limited, palliative effects. One treatment that is emerging as a potential panacea for the management of diabetes is *Gymnema sylvestre*. Yet, what evidence is there to support the use of this extract? In order to answer this question, a systematic review of the literature and a discussion of the best available evidence on gymnema are needed. The findings of such a review are presented in this paper.

INTRODUCTION

Diabetes mellitus is a disorder of carbohydrate, fat, and protein metabolism, characterized by chronic hyperglycemia[1] and the development of chronic, severe complications. At present, it is estimated that 150 million people across the globe have diabetes,[2] with the number expected to increase to 366 million by the year 2030.[3] Given this rise in the prevalence of diabetes, the myriad associated complications, and the shortfalls of existing treatment options, more effective interventions need to be sought.

In view of the fact that more than 800 plants have traditionally been used for the treatment of diabetes,[4] and that most plants have a spectrum of clinical effects, it can be speculated that the field of phytomedicine may offer an innovative solution to this chronic disorder. Yet, according to an earlier review of herbs and nutrient supplements that were claimed to improve glycemic control, few plants were supported by rigorous clinical evidence.[5] The herbs that did demonstrate positive clinical effects were gymnema (*Gymnema sylvestre* (Retz.) R.Br. ex Schult.), ivy gourd (*Coccinia indica* Wight & Arn.), bitter melon (*Momordica charantia* L.), aloe vera (*Aloe vera* (L.) Burm. f.), American ginseng (*Panax quinquefolius* L.), and gracemere-pear (*Opuntia streptacantha* Lem.). Of particular interest was the herb gymnema, because of its long history as a treatment for diabetes, and its range of unique and varied effects. Before the clinical effects of gymnema are discussed in detail, however, it is important to first examine the etiology, implications, and current management of diabetes to better understand why *G. sylvestre* may be a potentially useful treatment for diabetes mellitus.

IMPLICATIONS OF DIABETES MELLITUS

Taking into account the increasing prevalence of diabetes across the globe, as well as the associated complications of the disease, it is likely that diabetes will consume a significant proportion of health care resources in the future.[2,6] For example, diabetes mellitus is associated with myriad complications, including diabetic nephropathy, retinopathy, peripheral neuropathy, autonomic dysfunction, erectile dysfunction, atherosclerosis, hypertension, microvascular disease, and increased susceptibility to infection.[1,7] Each of these complications is associated with a reduction in quality of life and an increase in individual morbidity and mortality. In fact, compared to nondiabetic people, individuals with diabetes have a two- to fourfold greater risk of cardiovascular disease, a fivefold increased risk of blindness, four times the rate of kidney disease, three times the incidence of destructive periodontal disease,[8] and an increased rate of depression.[9]

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Given the above figures, it is therefore not surprising that in Australia in 2000–2001, the estimated cost of managing diabetes and its complications amounted to AUD$784 million (USD$447 million),[10] and in the United States in 2002, to USD$132 billion.[11] Recent figures suggest that a substantial part of this cost may be attributed to the use of key health care services.[8] Therefore, in view of rising budgetary restraints, staff shortages, spiraling health care expenses, and the costs of managing diabetes, it would not be sustainable to continue managing diabetes using existing treatment options. Instead, new treatments that effectively manage a number of etiological factors of the disease, which also provide long-term benefits to the patient and community, need to be developed or sought.

ETIOLOGY OF DIABETES

Many factors are believed to be responsible for the pathogenesis of diabetes, including age, ethnicity, genetics, obesity, autoimmunity, reduced physical activity, pancreatic β-cell defects, insulin resistance, and low-grade inflammation. Increasing age, for instance, is associated with a greater incidence of type 2 diabetes.[6] It is believed that advancing age may contribute to the development of insulin resistance and diabetes through increased visceral adiposity, elevated cellular triglyceride levels, and increased numbers of proinflammatory proteins.[6,10] The role of these inflammatory mediators in the development of diabetes in particular has been supported in epidemiologic, experimental and clinical studies, with an increase in the leukocyte count and the level of inflammatory markers released from adipose tissue found to predict the development of type 2 diabetes.[7,12,13]

As highlighted above, elevated lipid levels, particularly free fatty acids, as well as obesity and reduced physical activity, may all contribute to the development of insulin resistance. Other theories explaining the pathogenesis of insulin resistance also exist, including a reduction in glycogen synthase activity[14] and a decrease in the number of insulin receptors on the plasma membranes of adipocytes and skeletal muscle cells.[1,7] A genetic predisposition to glucose intolerance may also be responsible for the development of diabetes.[7]

Although the abovementioned enzymatic and target cell defects are likely to play an important role in the pathogenesis of diabetes, a factor that is key to the development of this disorder is impaired pancreatic beta cell activity. To illustrate, individuals without β-cell defects can compensate for insulin resistance indefinitely[6]; however, once insulin secretion falls to a level that can no longer compensate for insulin resistance, type 2 diabetes is likely to develop. Thus, the preservation of β-cell function is critical to attenuating the development of diabetes. Therefore, given that beta cell activity and β-cell mass may both decline in the presence of hyperglycemia and hypertriglyceridemia through a possible glucolipotoxic effect,[15,16] it is possible that β-cell function could be preserved through early and effective control of blood glucose and blood lipids. However, even though such a claim is supported by experimental research findings,[17] data from clinical studies are inconsistent, and therefore require further investigation.

Although many of the complications of diabetes are connected to a state of prolonged hyperglycemia and subsequent protein glycosylation, coagulation defects, tissue ischemia and hypoxia, and the accumulation of intracellular sorbitol,[9] the fall in endogenous insulin levels from impaired pancreatic β-cell activity may also be responsible, because insulin has been shown in a number of small studies to prevent platelet aggregation, facilitate vasodilatation, and to decrease the generation of reactive oxygen species.[16] Thus, in view of the abovementioned etiological factors, it is argued that a low-glycemic load diet and increased physical activity, in conjunction with interventions that reduce blood lipids, stimulate the activity of glycogen synthase, improve β-cell activity and insulin secretion, or reduce insulin resistance early in the disease, may prevent or delay the development of type 2 diabetes, and equally important, reverse the effects of the disease.[18] However, as highlighted in the following section, the majority of diabetes treatments to date fail to target more than one of these parameters.

CURRENT MANAGEMENT OF DIABETES MELLITUS

Existing treatments of diabetes mellitus, such as insulin and oral hypoglycemic agents, have generally been directed at addressing the relative deficit in insulin secretion or problems with insulin sensitivity. Even though these treatments improve glycemic control, and in effect, reduce the risk of complications,[9] these interventions are associated with a number of adverse effects,[19] and more importantly, are only palliative solutions to the problem, because many patients still require ongoing care, monitoring, and treatment for complications, resulting in an overconsumption of limited resources. Furthermore, these treatments place a major economic burden on the health care system, with the total cost of these antidiabetic medications in Australia, for instance, amounting to more than AUD$193 million (USD$148 million) in 2003–2004.[20]

New developments in the treatment of diabetes have begun to focus more specifically on the etiology of the condition, such as the decrease in the total number of pancreatic β-cells, in an attempt to "cure" the condition. One of these approaches is islet-cell transplantation. However, given the invasive nature of the procedure, the high cost, limited accessibility to all populations, the limited supply of islet cells, the need for technical expertise, and the risk of infection, malignancy, rejection, and autoimmune destruction,[21] other safer and more cost-effective treatments that target a number of etiologies of diabetes mellitus need to be

considered. One treatment that is showing promise in controlled clinical trials, and a herb that is most frequently prescribed by herbalists for improving glycemic control,[22] is *Gymnema sylvestre* (gymnema).

GYMNEMA

Definition

Gymnema, or gurmar, is a large woody climbing plant found in central and southern India, tropical Africa, and tropical Australia.[23] In the Ayurvedic system of medicine, gymnema is referred to as "mesasrngi," and both the dried leaf (mesasrngi leaf) and dried root (mesasrngi root) are used therapeutically.[24] The leaves of the plant in particular are used as a digestive, antiviral, diuretic, antiallergic, hypoglycemic, hypolipidemic, and antiobesity agent[25] for the treatment of diabetes, obesity, and dental caries. According to the Ayurvedic Pharmacopoeia of India,[24] both the dried leaf and root of gymnema, depending on dosage form and formulation, are also used in the treatment of svasa (bronchial asthma), kasa (cough), kustha (leprosy and other skin diseases), and vrana (wounds), among other conditions. Although the administration of gymnema for some of these conditions has since been supported by experimental research findings,[26] the key active constituents of the plant remain poorly elucidated.

The main constituent of gymnema is believed to be gymnemic acid, a mixture of at least 17 different saponins. It is this acid that is commonly used as a marker for standardization and quality control in most commercial preparations of gymnema. However, a number of other chemical constituents have also been identified in *G. sylvestre.* The gymnemasaponins, for instance, are another major component of gymnema, of which there are at least seven different types.[26] These constituents, as well as the polypeptide Gurmarin, the alkaloid conduritol, gymnamine, gypenoside, and the dammarane-type saponins gymnemasides 1–5 and gymnemasin B, C, and D are all likely to be responsible for the hypoglycemic and antisaccharin effect of the plant.[26] Thus, without further investigation into the chemistry of Gymnema, as well as the effects of each constituent, it is difficult to establish which markers are likely to be the best indicators of quality and efficacy.

METHODS OF SYSTEMATIC REVIEW

A comprehensive search of the literature was conducted in April 2006 to identify the best available evidence on *G. sylvestre* and diabetes mellitus. The search used the following databases: AARP Ageline, Allied and complementary medicine, Australasian Medical Index, BioMed Central Gateway, CAM on PubMed, CENTRAL, CINAHL, Cochrane library, Current contents connect, Current controlled trials, Database of Abstracts of Reviews of Effectiveness, Dissertations Abstracts International, EMBASE, Health source nursing/academic edition, International Pharmaceutical Abstract, MEDLINE,® and Turning Research Into Practice. The key terms used in the search were Asclepiadaceae, clinical trial, controlled clinical trial, diabetes mellitus, double-blind method, glucose intolerance, Gurmar, Gymnema, *Gymnema sylvestre*, insulin resistance, metabolic syndrome x, placebo, prospective studies, randomized controlled trial, single-blind method, and type 1 and type 2 diabetes. The search was limited to randomized controlled trials that used orally administered monopreparations of *G. sylvestre* for glycemic control. Combination or homeopathic preparations of gymnema and studies with insufficient detail were excluded from the review.

RESULTS OF SYSTEMATIC REVIEW

A total of two clinical trials that met the inclusion criteria were identified in the search, however, both trials were open-label comparative studies.[27,28] Furthermore, using the Joanna Briggs Institute critical appraisal of evidence of effectiveness tool, both trials had an appraisal score of only 3/11, meaning that both studies had a high level of bias. Thus, given that no clinical trials were of good quality, statistical pooling of results was not appropriate. Therefore, this paper can only provide a narrative review of ***G. sylvestre*** and diabetes mellitus.

DISCUSSION

Much of the research on gymnema has looked at the hypoglycemic effects of the plant. These studies have demonstrated that gymnema may exert its antidiabetic effect via a number of pathways. Some of these effects are similar to those produced by existing oral hypoglycemic agents, whereas some are unique. Experimental studies, for instance, have found that many of the constituents in gymnema decrease the uptake of glucose from the small intestine.[26] In rabbits, gymnema has also demonstrated improvements in glycogen synthesis, glycolysis, gluconeogenesis, and hepatic and muscle glucose uptake,[29] as well as the reversal of hemoglobin and plasma protein glycosylation.[30] Some authorities also indicate that gymnema may improve glycemic control by stimulating insulin release from the pancreatic islets of Langerhans.[27] To investigate this claim, Srivastava et al.[31] examined the hypoglycemic and life-prolonging effects of four different single doses (0.2 g, 0.4 g, 0.6 g, and 0.8 g) of an aqueous extract of dried *G. sylvestre* leaves in rats with moderate (blood glucose 150–200 mg/dL), severe (blood glucose 250–400 mg/dL), and toxic (blood glucose >400 mg/dL) alloxan-induced diabetes. The greatest re-

duction in blood glucose levels, and the greatest effect on longevity, was observed in the moderately diabetic rats administered gymnema at a dose of 0.6 g. Doses of gymnema extract above 0.6 g offered no additional improvement in blood glucose control. A particularly important finding was that the efficacy of gymnema was inversely related to the severity of diabetes, a finding supported in a similar study using 0.4 g of an aqueous extract of *G. sylvestre* leaves daily for a period of 2 weeks.[32] Thus, it is possible that partial pancreatic β-cell activity may be required for gymnema to exert an antidiabetic effect. Yet, as illustrated in the following study, gymnema may be capable of improving β-cell activity, and therefore, such a claim requires further investigation.

In a study by Shanmugasundaram et al.,[33] both normal and streptozotocin-treated rats were treated with either a 50% ethanolic extract of gymnema leaves (GS_3, 20 mg/day/rat), a purified residue of GS_3 (GS_4, 20 mg/day/rat), or no intervention for up to 95 days. When compared to untreated diabetic rats, both GS_3- and GS_4-treated diabetic rats demonstrated a 30% increase in total pancreatic weight, as well as a significant increase in the number of islets ($p < 0.001$) and number of β-cells per islet ($p < 0.05$). The regeneration of pancreatic tissue resulted in complete control of fasting blood glucose levels within 60 and 20 days in the GS_3 and GS_4 groups, respectively. Unlike sulphonylurea medication, however, gymnema extract did not increase insulin release in normal rats under normoglycemic conditions. Thus, as demonstrated in several other studies,[30,34] it is likely that gymnema has a normalizing effect on blood glucose, and may therefore be safer than conventional oral hypoglycemic agents. Although the comparative safety of gymnema and other oral hypoglycemic agents have yet to be explored clinically, findings from a recent experimental study indicate that gymnema is at least comparable to the standard hypoglycemic agent tolbutamide in reducing blood glucose levels.[35]

A number of additional explanations for the mechanism behind the hypoglycemic effect of gymnema have also been reported in the literature, including an antagonistic effect on somatotropin-, corticosteroid-, and adrenaline-induced hyperglycemia[31]; attenuation of the insulinotropic action of gastrointestinal hormones; and an increase in peripheral insulin sensitivity.[34] Yet, as with the abovementioned actions, there are insufficient clinical data to validate these claims. Even though the pharmacokinetic mechanisms of gymnema are still under investigation, data from clinical trials suggest that gymnema may at least be useful in improving glycemic control.

In one open-label trial, 65 patients with type 1 and type 2 diabetes were each treated with *G. sylvestre* leaf extract, 400 mg b.i.d. for 90 days.[36] The study found that when compared to baseline values, preprandial blood glucose level (BGL), postprandial BGL and HbA1c decreased by 11%, 13%, and 0.6%, respectively. These reductions in fasting BGL and postprandial BGL are further supported by two small, nonrandomized, open-label trials of patients with diabetes, of which 6–10 g of gymnema leaf extract were administered for 15–21 days.[37,38]

Additional support for the efficacy of gymnema in both type 1 and type 2 diabetes comes from two earlier controlled, open-label trials, where the effects of gymnema extract (400 mg GS_4 daily) and conventional therapy were compared to conventional therapy alone. The first trial examined the effects of gymnema extract on 22 patients with type 2 diabetes for 18–20 months.[27] Compared to baseline data, gymnema significantly reduced blood glucose ($p < 0.001$), glycosylated hemoglobin ($p < 0.001$), and glycosylated plasma proteins ($p < 0.001$) over the 18–20-month period, whereas under conventional treatment (glibenclamide or tolbutamide, $n = 25$), these values increased or remained unchanged. In the second trial, the effect of gymnema extract on 27 patients with type 1 diabetes was explored for 6–30 months.[28] Compared with baseline data, gymnema significantly reduced glycosylated plasma protein ($p < 0.001$) in the first 6–8 months, and serum amylase ($p < 0.001$) at 16–18 months. In comparison to conventional therapy (insulin, $n = 37$), gymnema significantly increased serum C-peptide levels within 16–18 months ($p < 0.001$). The conventional treatment group, on the other hand, demonstrated no significant improvement in glycemic control during the treatment period. Similarly, although patients taking gymnema in both studies reported an improvement in well-being, alertness and exhaustion, and a decrease in the dose of conventional treatment during the trial, no improvement in either of these parameters was evident in the conventional therapy group. Although these findings suggest that gymnema may be effective in improving glycemic control in patients with diabetes, the lack of rigor and the poor methodological quality of these studies limit any conclusions that can be made.

CONCLUSIONS

The prevalence and incidence of diabetes mellitus is rising worldwide. This increasing trend, as well as the significant rise in associated morbidity and mortality, is likely to have a profound impact on families, communities, health care resources, and funding. Thus, new cost-effective interventions that effectively manage the disease need to be sought. Given that *G. sylvestre* targets several of the etiological factors connected with diabetes (Fig. 1), including chronic inflammation,[39] obesity,[40,41] enzymatic defects, and pancreatic β-cell function,[33] and no single oral hypoglycemic drug presently exerts such a diverse range of effects, suggests that gymnema may be useful in the management of diabetes and the prevention of associated pathological changes. However, as this systematic review shows, the clinical efficacy of gymnema has only been supported by a small number of nonrandomized, open-label trials. Hence, further investigation into the clinical effect of *G. sylvestre* on both diabetes and its associated complications is urgently needed.

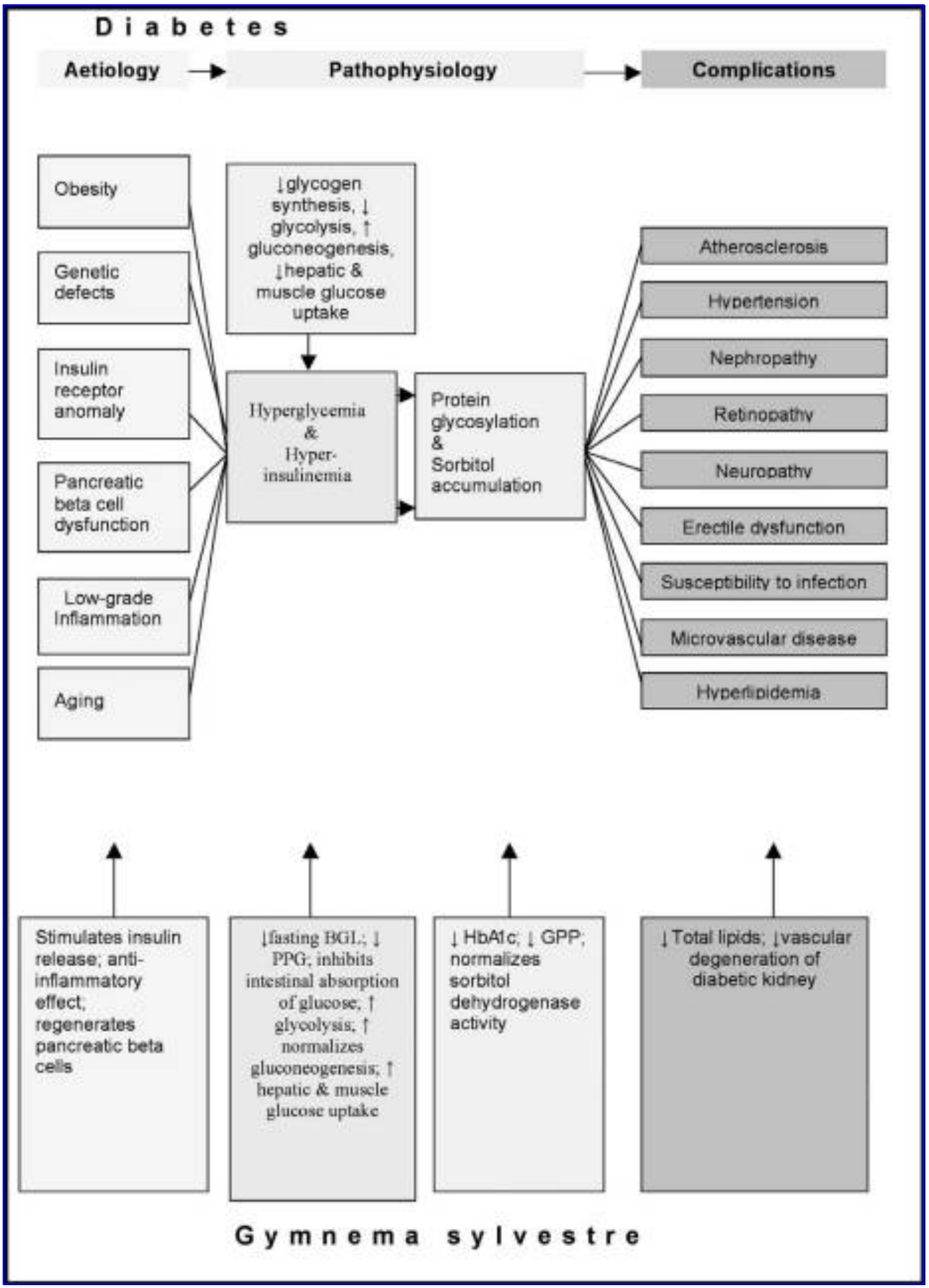

FIG. 1. The development of type 2 diabetes mellitus, and the reported effects of *Gymnema sylvestre* on various processes of the disease. BGL, blood glucose level; GPP, glycosylated plasma proteins; HbA1c, glycosylated hemoglobin A1c; PPG, postprandial glucose.

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